

# DRUG INTERACTIONS

## Impact of perampanel on pharmacokinetics of concomitant antiepileptics in patients with partial-onset seizures: pooled analysis of clinical trials

**Correspondence** Dr Oneeb Majid, Associate Director, Clinical Pharmacology, Eisai Europe Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire AL10 9SN, UK. Tel.: +44 845 676 1400; Fax: +44 845 676 1401; E-mail: oneeb\_majid@eisai.net

**Received** 20 November 2015; **revised** 7 March 2016; **accepted** 26 March 2016

Oneeb Majid<sup>1</sup>, Antonio Laurenza<sup>2</sup>, Jim Ferry<sup>3</sup> and Ziad Hussein<sup>1</sup>

<sup>1</sup>Clinical Pharmacology, Eisai Europe Ltd., Hatfield, Hertfordshire, UK, <sup>2</sup>Neuroscience and General Medicine PCU, Eisai Inc., Woodcliff Lake, New Jersey, USA and <sup>3</sup>Clinical Pharmacology, Eisai Inc., Woodcliff Lake, New Jersey, USA

**Keywords** carbamazepine, clearance, concomitant AEDs, CYP3A4/5, drug interactions, oxcarbazepine

### AIMS

To evaluate the impact of perampanel and demographics on clearance of concomitant antiepileptic drugs (AEDs), in patients with refractory partial-onset seizures.

### METHODS

Pooled data from three Phase III clinical studies with adjunctive perampanel were used. Blood samples for evaluation of 11 concomitant AEDs were taken during baseline (before perampanel initiation), and at weeks 10, 14, and 19 during the maintenance phase of perampanel treatment (2–12 mg/day, once daily at bedtime). Models estimating apparent clearance of each concomitant AED were fitted to the data, and the effects of perampanel and demographic variables on clearance were determined. Final models were assessed with goodness of fit plots including population predictions and individual predictions against observations.

### RESULTS

No significant impact of perampanel on clearance was found for clonazepam ( $n = 81$ ), levetiracetam ( $n = 330$ ), phenobarbital ( $n = 54$ ), phenytoin ( $n = 90$ ), topiramate ( $n = 226$ ) or zonisamide ( $n = 93$ ). Statistically significant, but small and not clinically relevant increases in model-predicted clearance were detected for carbamazepine (+4.3% with 12 mg perampanel;  $n = 379$ ), clobazam (+3.4% males, +7.7% females, 12 mg;  $n = 114$ ), lamotrigine (+9.3%, 12 mg;  $n = 356$ ), and valproic acid (+5.0%, 12 mg;  $n = 349$ ). Oxcarbazepine clearance was reduced (26%;  $n = 200$ ), but the clinical relevance is unclear as levels of the active metabolite (the monohydroxy derivative of oxcarbazepine) were not measured.

### CONCLUSIONS

Population PK data show that perampanel (2–12 mg/day, once daily at bedtime) has no relevant impact on the clearance of the most commonly used concomitant AEDs.

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Perampanel is an adjunctive treatment for partial-onset, and primary generalized tonic–clonic seizures.
- *In vitro* work indicated a low potential for significant effects of perampanel on CYP or UGT enzymes.
- Perampanel has been reported to affect the exposure of some AEDs and non-AEDs in a limited number of patients. Therefore, we report full PK models for the impact of perampanel on 11 concomitant AEDs in a Phase III study population.

## WHAT THIS STUDY ADDS

- Perampanel does not affect the clearance of most commonly used concomitant AEDs in a clinically relevant way, in patients with partial-onset seizures.
- While perampanel is associated with a small reduction in oxcarbazepine clearance, the clinical relevance is not clear.

## Introduction

Perampanel is an antiepileptic drug (AED) approved for adjunctive treatment of partial-onset and primary generalized tonic–clonic seizures in patients aged 12 and above [1, 2]. Phase III data in partial-onset seizures [3–5] and primary generalized seizures [6] have been reported, and several pharmacokinetic (PK) and PK/pharmacodynamic (PD) analyses of healthy volunteer and patient populations have been reported [7].

*In vitro* data in hepatocytes shows that perampanel is metabolized predominantly by cytochrome P450 (CYP) isotype CYP3A4/5 [7], and therefore its clearance could be affected by AEDs (and other drugs) that inhibit or induce CYP3A4/5 – this has been extensively characterized and reported in PK analyses in epilepsy patient populations [1, 2, 8, 9]. When the effect of perampanel on other drugs was explored, perampanel was found to have only weak inhibitory effects *in vitro* on CYP (CYP2C8, CYP3A4) and uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A9, UGT2B7), to weakly induce CYP2B6, CYP3A4/5, UGT1A1 and UGT1A4, and was not a substrate or inhibitor of drug transporters *in vitro* [1, 2, 7]. Consequently, perampanel was not expected to cause a clinically important effect on the PK of other drugs. Contrary to these expectations, perampanel, at the highest approved clinical dose of 12 mg/day, reduces exposure of the progesterone component of the contraceptive pill. In a healthy volunteer study, 48 women took perampanel or placebo concomitantly for 21 days, with an oral combined contraceptive pill (Microgynon®) [7]. Perampanel, at its highest recommended dose of 12 mg ( $n = 8$ ), but not at doses of 8 or 4 mg/day, was shown to reduce mean  $C_{max}$  and AUC of levonorgestrel by 40% vs. control, with minimal effects on the ethinylestradiol component (18% reduction in AUC) [7]. This effect has not been explored further in a wider clinical population, and the mechanism is as yet unknown.

In light of this finding, it is important to confirm the expectation that perampanel has no perpetrator effects on other AEDs, and this was addressed via population-based modelling of data obtained in three Phase III studies of perampanel in patients with refractory partial seizures. The impact of perampanel on the clearance of concomitant AEDs is briefly summarized in product labels [1, 2], but the modelling process and results have not previously been reported in full. Here we report these data – the final models for each concomitant AED, and the impact on the clearance of each AED of adjunctive perampanel and demographics in the Phase III PK population of patients with refractory partial-onset seizures.

## Methods

### Design

The population was derived from three Phase III, multicentre, randomized, placebo-controlled trials of adjunctive perampanel [3–5]. A 6-week pre-randomization phase was followed by a 19-week double-blind phase, which comprised a 6-week titration phase and a 13-week maintenance phase. Patients who completed the study then either had a follow-up visit, or entered an open-label extension study [10, 11]. Data for this analysis was obtained from the 13-week maintenance phase.

### Participants

The patient population is described in full elsewhere [3–5, 10]. Briefly, patients were aged  $\geq 12$  years, with partial-onset seizures that were not controlled despite treatment with  $\geq 2$  AEDs in the past 2 years. Patients could receive up to three concomitant AEDs in addition to perampanel or placebo, providing doses were stable, and only one was an enzyme-inducing AED (EIAED). When the studies began, carbamazepine, phenytoin, phenobarbital, and primidone were defined as EIAEDs; however, subsequent analysis of the Phase III studies showed that perampanel clearance was in fact induced to a clinically relevant extent by carbamazepine, oxcarbazepine and phenytoin only [1, 12].

The AED PK population included all patients in the intent-to-treat (ITT) populations who had: at least one quantifiable AED plasma concentration data point at baseline and another during the maintenance phase; complete dosing and sampling history; adequate concomitant AED information; and no protocol deviation that might have affected exposure.

Each of the Phase III clinical trials was performed in accordance with the Declaration of Helsinki, Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, European Directive 2001/83/EC and US Code of Federal Regulations Title 21. Trial protocol, amendments and informed consent were reviewed by national regulatory authorities in each country and independent ethics committees or institutional review boards for each site. Before participation, all patients gave written informed consent [3–5].

### Treatments

The study drug (perampanel or matched placebo) was instructed to be dosed daily at bedtime. Information on concomitant AED dosing was recorded in the case report form. Inconsistencies

were identified in some patients between recorded concomitant AED dosing and blood samples (e.g. missing or zero plasma concentrations for AEDs recorded as being taken concomitantly); subjects with inconsistent information were excluded from the AED population PK analyses.

### Analytical methods

Two blood samples, taken 1–2 hours apart and approximately 10 hours and beyond after the evening dose of perampanel, were taken by venipuncture for assessment of perampanel concentration and of concomitant AED concentrations at visits 6, 7 and 8 (weeks 10, 14 and 19, during the maintenance phase). Additionally, single blood samples were taken for assessment of concomitant AED concentrations before the initiation of perampanel treatment at visit 1 (start of baseline) and visit 2 (start of titration, before the perampanel first dose); and also after early discontinuation or at study completion (follow-up visit), if patients did not enter the extension study. The exact timing of PK sampling relative to dose of concomitant AEDs is not reported, as time-variant models were not fitted to the data.

The total plasma concentration of each of the 19 concomitant AEDs was determined using validated assay methods, utilizing liquid–liquid extraction followed by high performance liquid chromatography with tandem mass spectrometry. All the bioanalytical assays were performed by Frontage Laboratories, Exton, Pennsylvania, USA. Accuracy and precision were within  $\pm 15\%$  for low-, mid- and high-level concentrations except at the lower limit of quantitation, where  $\pm 20\%$  was permitted based on laboratory standard operating procedures and FDA Guidance for Industry on Bioanalytical Methods Validation, May 2001. Assay interference was tested for all AEDs on perampanel and *vice versa*, with no impact.

For the data analysis, plasma concentrations were included only for the AEDs that were taken by at least 30 patients each: carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid and zonisamide. Because the PK sampling was sparse, a sufficient number of subjects were required to adequately characterize the PK of each AED. A minimum of 30 subjects per AED was considered appropriate. Therefore, although plasma concentrations were measured for the following concomitant AEDs, they were not included in the data analysis because they were taken by fewer than 30 patients: acetazolamide, diazepam, felbamate, gabapentin, pregabalin, primidone, rufinamide and tiagabine.

### PK modelling

**PK model and parameters.** Due to the sparse nature of the data and having only two samples at each visit, 1–2 hours apart, and missing information on the dosing time of the concomitant AEDs, the estimation of complete compartmental PK modelling could not be utilized. Instead, a model estimating the apparent clearance as the ratio of the rate of input and the measured concentration was fitted to the data. The effect of perampanel and intrinsic and extrinsic covariates on the clearance of each AED was determined, and declared statistically significant if  $P < 0.01$  (a decrease in objective function of at least 6.64) and the

95% confidence interval (CI) for the effect parameter did not include unity.

For all AEDs except phenytoin, a simple model was fitted to the data, assuming the observed concentration as a steady-state concentration, close to the  $C_{avss}$  over a dosing interval, using the relationship:

$$C_{avss} = \frac{R_0}{CL}$$

where  $R_0$  = total daily dose per 24 hours.

For phenytoin, a Michaelis and Menten model using  $V_{max}$  (maximal velocity) and  $K_m$  (Michaelis constant) was fitted to the data.

For each concomitant AED, the following covariates were investigated for their effect on apparent clearance: age, race, weight, fat body mass (FBM), lean body mass (LBM), body mass index (BMI), gender, concomitant medications, creatinine clearance and liver function enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]).

Variability in the apparent clearance ( $CL/F$ ) between subjects was estimated using an exponential model. Inter-occasion variability was defined for visits 1, 2, 6, 7 and 8 as five distinct but identical occasions. The variance of the residual error was estimated with either a combined proportional with additive error model or only proportional. The first-order conditional estimation method with interaction (FOCEI) estimation method was used.

Goodness of fit plots of the final model included: scatter plots of the population predictions (PRED) vs. observations, on linear and log scales; scatter plots of the individual predictions (IPRED) vs. observations, on linear and log scales; and scatter plots of the weighted residual (WRES) vs. population predictions (PRED).

The covariate selection was conducted as follows:

1. A model including all demographic covariates of interest, AST, ALT and creatinine clearance was estimated, all redundant covariate parameters removed using backward deletion using the likelihood ratio test (LRT) at  $P < 0.001$ .
2. Then all potential AEDs (excluding perampanel) were added to the resulting model, and submitted to backward deletion until no redundant AED was present in the model.
3. The final model from step 2 was used to investigate the effect of perampanel (yes/no), perampanel dose and concentrations on the clearance of the given AED. Linear, log-linear and  $E_{max}$  (maximum effect on PD assessment) models were used to test the effect of perampanel.

**Clinical relevance.** The clinical relevance of any effect of perampanel on AED clearance was determined by considering the magnitude of the effect on clearance in conjunction with the inter-individual variability (IIV) in clearance. If the effect size was within the magnitude of IIV, the effect was considered not to be clinically relevant. The strength of any effect on clearance was also considered within the guidance from the Food and Drug Administration (FDA) on drug interactions. They classify 'weak' inhibitors as those that cause a 20–50% decrease in clearance or 1.25- to <2-fold increase in AUC, and 'weak' inducers as those that cause a 20–50% decrease in AUC [13].

**PK model qualification.** The simulated and observed data were represented as a function of the time after dosing, rounded to the closest hour; i.e., data were summarized by bins of 1 hour. In addition, the observed data and 5th and 95th percentile limits were presented graphically overall, by dose and by visit.

## Results

The PK population for concomitant AED analysis had broadly consistent demographics for each concomitant AED studied: carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid and zonisamide (Table 1). As patients could take up to three concomitant AEDs, these groups are not mutually exclusive.

### Observed AED plasma concentration by visit

Box/whisker plots of observed plasma concentrations of each concomitant AED by visit (before and during perampanel treatment) are shown in Figure 1. Little change is seen between median plasma concentration of any AED between the two pre-perampanel measurements (visit 1 = baseline; visit 2 = first day of titration, before perampanel dosing) and during perampanel treatment (visits 6, 7 and 8 = weeks 10, 14 and 19 during the maintenance phase).

### Model-predicted clearance of concomitant AEDs

The model-predicted clearance of each concomitant AED, in the presence and absence of perampanel, is shown in Table 2. The clearance of some concomitant AEDs was significantly affected by gender or by other concomitant

AEDs (e.g. phenytoin); clearance is therefore shown separately for these subgroups where necessary. The impact of demographic covariates on AED clearance is shown in the Supplemental Material.

**Clearance not significantly altered by perampanel.** Our modelling found no significant effect of perampanel on the clearance of the following AEDs, and the 95% CIs included unity: clonazepam (Figure 1C), levetiracetam (Figure 1E), phenobarbital (Figure 1G), phenytoin (Figure 1H), topiramate (Figure 1I) and zonisamide (Figure 1K).

Full details of the final PK model for each concomitant AED are shown in Supplemental Tables S1 to S11. Apparent clearance of clonazepam, in the final model, was increased when co-administered with phenytoin, valproic acid and clobazam (Supplemental Table S3); levetiracetam clearance increased with body weight, and was lower in female subjects and in subjects co-administered phenytoin or valproic acid (Supplemental Table S5); phenobarbital clearance was greater in subjects with AST or ALT greater than two times the upper limit of normal, and lower in subjects co-administered lamotrigine or oxcarbazepine (Supplemental Table S7); phenytoin clearance increased with an increase in its daily dose and was greater in subjects co-administered oxcarbazepine or zonisamide (Supplemental Table S8); topiramate clearance increased with body weight and was greater in subjects co-administered phenytoin or zonisamide (Supplemental Table S9); and zonisamide clearance increased in the presence of phenytoin and phenobarbital and was lower in subjects treated with clobazam (Supplemental Table S11).

**Clearance significantly altered by perampanel, but not clinically relevant**

**Carbamazepine.** In the final model ( $n = 379$  total,  $n = 269$  with perampanel), carbamazepine dose and valproic acid

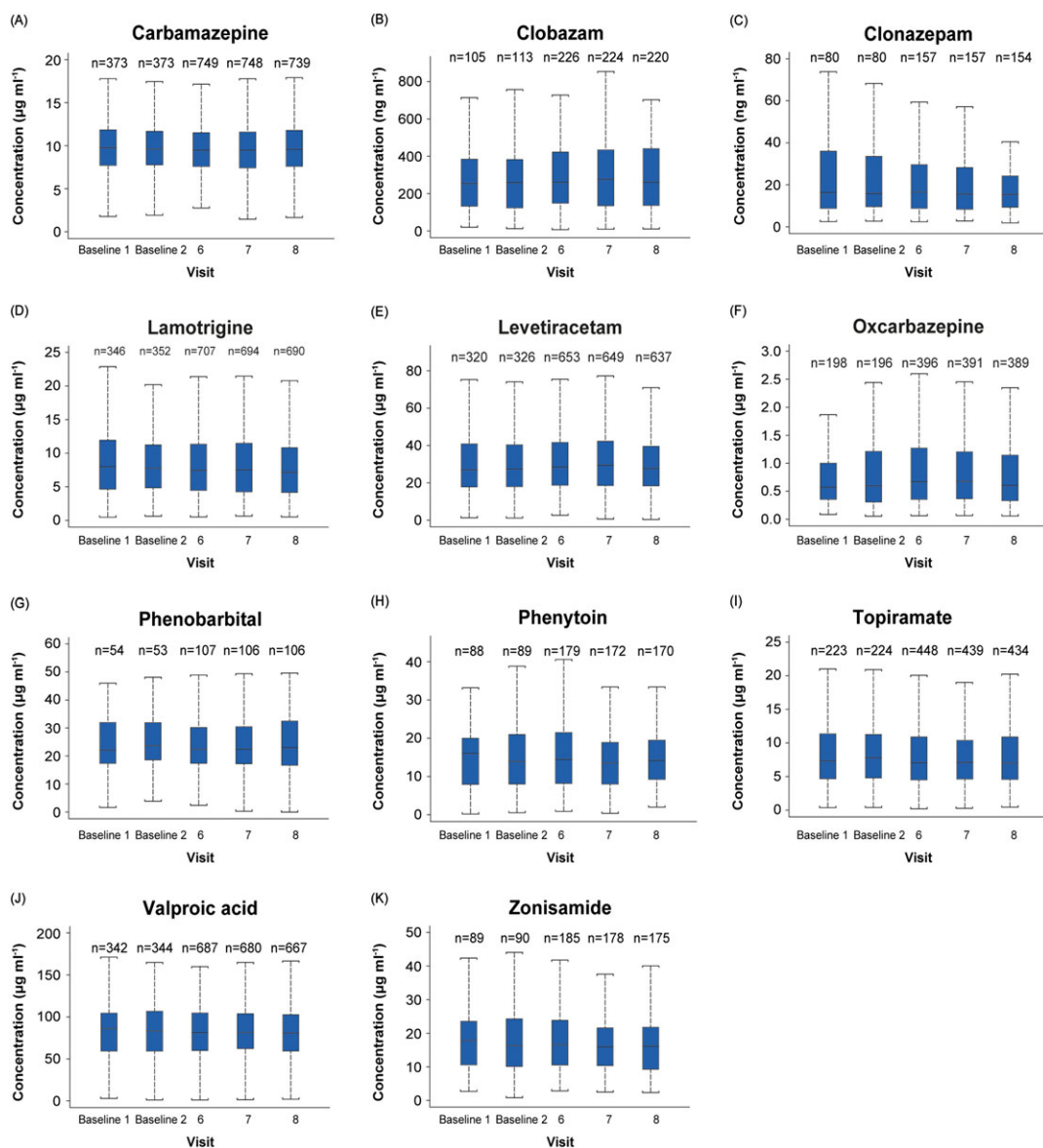
**Table 1**

Demographics by concomitant AED in perampanel Phase III PK population

AED	n	Mean age, yrs (SD)	Mean weight, kg (SD)	Male gender, n (%)	Ethnicity, n (%)				
					White	Asian	Chinese	Black	Other*
<b>CBZ</b>	379	33.5 (12.8)	68.2 (17.7)	183 (48.3)	269 (71.0)	61 (16.1)	36 (9.5)	2 (0.5)	11 (2.9)
<b>CLB</b>	114	32.8 (12.9)	67.9 (17.3)	56 (49.1)	76 (66.7)	31 (27.2)	3 (2.6)	0	4 (3.5)
<b>CLN</b>	81	35.6 (13.3)	71.2 (19.0)	33 (40.7)	68 (84.0)	4 (4.9)	6 (7.4)	0	3 (3.7)
<b>LTG</b>	356	34.7 (12.5)	73.1 (17.3)	166 (46.6)	283 (79.5)	32 (9.0)	25 (7.0)	7 (2.0)	9 (2.5)
<b>LEV</b>	330	35.3 (13.6)	72.3 (17.9)	158 (47.9)	265 (80.3)	29 (8.8)	19 (5.8)	12 (3.6)	5 (1.5)
<b>OXC</b>	200	33.8 (13.8)	73.4 (17.6)	98 (49.0)	156 (78.0)	22 (11.0)	10 (5.0)	6 (3.0)	6 (3.0)
<b>PHB</b>	54	36.6 (14.2)	72.0 (22.8)	25 (46.3)	37 (68.5)	11 (20.4)	4 (7.4)	1 (1.9)	1 (1.9)
<b>PHT</b>	90	36.4 (15.1)	75.0 (19.9)	56 (62.2)	57 (63.3)	16 (17.8)	7 (7.8)	7 (7.8)	3 (3.3)
<b>TPM</b>	226	33.6 (13.7)	68.0 (18.0)	112 (49.6)	174 (77.0)	23 (10.2)	19 (8.4)	4 (1.8)	6 (2.7)
<b>VPA</b>	349	32.5 (12.6)	68.6 (16.9)	196 (56.2)	234 (67.0)	54 (15.5)	46 (13.2)	4 (1.1)	11 (3.2)
<b>ZNS</b>	93	33.3 (13.0)	70.4 (19.0)	40 (43.0)	64 (68.8)	21 (22.6)	1 (1.1)	3 (3.2)	4 (4.3)

\*Other includes American Indian and Alaska native.





**Figure 1**

Box/whisker plots of concomitant AED concentration by visit, in patients taking perampanel concurrently with each AED. Box plots showing observed plasma c-oncentrations of concomitant AEDs by visit. Line: median concentration; box: 25–75th percentiles; whiskers:  $\pm 1.5 \times$  interquartile range;  $n$  = number of observations. Visits are as follows: Baseline 1: Start of 6-week baseline phase; Baseline 2: start of 6-week titration phase, on the day that (but before) the first perampanel dose is administered; visit 6: week 10 (maintenance); visit 7: week 14 (maintenance); visit 8: week 19 (last week of maintenance phase). Plots are arranged alphabetically, from carbamazepine (A) to zonisamide (K)

co-administration were significant covariates (Supplemental Table S1). In addition, perampanel co-administration increased carbamazepine clearance, proportional to perampanel dose and to carbamazepine clearance (final dose effect of perampanel: 0.00357, 95% CI 0.0001–0.0071; Supplemental Table S1). However, model-derived predictions of the effects of perampanel on carbamazepine clearance ( $3.5 \text{ l h}^{-1}$  without perampanel,  $3.60$ – $3.65 \text{ l h}^{-1}$  with perampanel; Table 2) indicated the magnitude of the perampanel effect is very small (clearance increased by 4.3% with 12 mg perampanel). The magnitude of this effect is very small and within the inter-subject variability – the effect is therefore not considered clinically relevant.

Clobazam. The model showed that perampanel was associated with an increase in clobazam clearance, proportional to perampanel concentrations and to clobazam clearance (final concentration-effect of perampanel 0.0000678, 95% CI 0.0000249–0.0001107; Supplemental Table S2). Model-derived predictions of the effects of perampanel on clobazam clearance show that in males, predicted clobazam clearance without perampanel is  $3.27 \text{ l h}^{-1}$ , and with perampanel ranges from  $3.36$  to  $3.38 \text{ l h}^{-1}$  (3.4% increase with 12 mg, Table 2). In females, predicted clearance without perampanel is  $1.43 \text{ l h}^{-1}$  and with perampanel ranges from  $1.52$  to  $1.54 \text{ l h}^{-1}$  (7.7% increase with 12 mg, Table 2). The small magnitude of the increase in clearance, along with the

**Table 2**

Impact of perampanel on model-predicted clearance of concomitant AEDs in Phase III PK population

Concomitant AED	Number of subjects		AED apparent clearance ( $\text{l h}^{-1}$ )			Variability	
	Taking AED	Taking AED + PER	Without PER	With PER		IIV* (%CV)	IOV† (%CV)
				8 mg	12 mg		
<b>CBZ</b>	379	269	3.50	3.60	3.65	22.6	15.7
<b>CLB (males)</b>	56	39	3.27	3.36	3.38	70.5	16.1
<b>CLB (females)</b>	58	40	1.43	1.52	1.54		
<b>CLN</b>	81	44	Not altered by perampanel			70.5	16.1
<b>LTG</b>	356	257	1.18	1.27	1.29	49.9	17.2
<b>LEV</b>	330	235	Not altered by perampanel			48.0	18.4
<b>OXC (males, no PHT)</b>	91	56	63.4	46.9		55.2	44.2
<b>OXC (females, no PHT)</b>	96	67	46.7	30.2			
<b>OXC (males, with PHT)</b>	7	6	115.6	98.9			
<b>OXC (females, with PHT)</b>	6	4	99.0	82.4			
<b>PHB</b>	54	37	Not altered by perampanel			53.0	13.7
<b>PHT</b>	90	68	Not altered by perampanel			62.7	22.8
<b>TPM</b>	226	162	Not altered by perampanel			46.0	17.1
<b>VPA</b>	349	246	0.60	0.62	0.63	56.2	17.5
<b>ZNS</b>	93	60	Not altered by perampanel			48.5	14.7

\*IIV (%CV): inter-individual variability (% coefficient of variation). †IOV (%CV): inter-occasion variability (% coefficient of variation). CBZ, carbamazepine; CLB, clobazam; CLN, clonazepam; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

lack of change in IIV between the base and the final model for clobazam, suggest that perampanel had no clinically important effect on clobazam PK.

Lamotrigine. In the final model, lamotrigine apparent clearance was increased by co-administration with carbamazepine and phenobarbital and decreased in subjects treated with valproic acid. In addition, perampanel increased lamotrigine clearance proportionally to the  $\log_e$  of perampanel daily dose (final estimate: 0.037; 95% CI 0.018–0.056; Supplemental Table S4). The model predicts a slight increase of lamotrigine clearance from 1.18  $\text{l h}^{-1}$  without perampanel, to 1.27–1.29  $\text{l h}^{-1}$  in the presence of perampanel (9.3% increase with 12 mg, Table 2). This effect was not considered clinically relevant.

Valproate. In the final PK model, valproic acid clearance increased with body weight and increased proportionally to perampanel dose (effect of perampanel dose: 0.00761, 95% CI 0.002–0.014; Supplemental Table S10). Model-derived predictions give valproic acid clearance of 0.60  $\text{l h}^{-1}$  without perampanel, and 0.62–0.63 with (5.0% increase with 12 mg, Table 2). The effect was not considered clinically relevant.

*Clearance altered by perampanel, potentially clinically relevant*  
Oxcarbazepine. Observed plasma concentrations of oxcarbazepine before and during perampanel treatment are

shown in Figure 1F. In the final model for oxcarbazepine, clearance was lower in females than males and increased when co-administered with phenytoin. Perampanel co-administration resulted in a 26% decrease in oxcarbazepine clearance, independent of perampanel dose or concentration (perampanel effect  $-0.261$ ; 95% CI  $-0.392$ – $-0.13$ ; Supplemental Table S6). Model-derived predictions of the effects of perampanel on oxcarbazepine clearance are shown in Table 2. The relevance of such changes is unknown since oxcarbazepine acts as a pro-drug to its major metabolite MHD, which has a different pharmacokinetic profile and was not measured in this study. However, the magnitude of the effect of perampanel dosing on oxcarbazepine clearance remains within both the estimated IIV of 55% and IOV of 41%.

### Metabolic pathways

A summary of the metabolic pathways of each concomitant AED, and the effect of perampanel on its clearance, is shown in Table 3.

### Discussion

Pre-clinical pharmacokinetic studies with perampanel indicated a low likelihood of clinically relevant perpetrator effects on other drugs: it was not a substrate or an inhibitor of drug

**Table 3**

Metabolic pathways and summary of perampanel effect on clearance for concomitant AEDs in Phase III PK population

Concomitant AED	Main route of elimination*	Effect of perampanel on CL/F of AED
<b>Carbamazepine</b>	Oxidation (CYP3A4)	<b>CL increases with dose:</b> 4.3% with 12 mg
<b>Clobazam</b>	Oxidation (CYP3A4)	<b>CL increases with dose:</b> 3.4% in males at 12 mg, 7.7% in females at 12 mg
<b>Clonazepam</b>	Oxidation (CYP3A4)	No effect
<b>Lamotrigine</b>	Conjugation (UGT1A4)	<b>CL increases with log(dose):</b> 9.3% with 12 mg
<b>Levetiracetam</b>	Hydrolysis (25%), renal excretion (75%)	No effect
<b>Oxcarbazepine</b>	Conjugation (>50%), renal excretion (>30%)	<b>CL decreases by 26%:</b> 26% reduction in males, no phenytoin, 35.3% reduction in females, no phenytoin 14.4% reduction in males, with phenytoin 16.8% reduction in females, with phenytoin
<b>Phenobarbital</b>	Oxidation/conjugation (CYP2C9, 2C19, 2E1), and renal excretion	No effect
<b>Phenytoin</b>	Oxidation (CYP2C9, 2C19)	No effect
<b>Topiramate</b>	Oxidation (20–60%), renal excretion (40–80%)	No effect
<b>Valproic acid</b>	Oxidation (CYP2A6, 2C9, 2C19, 2B6), conjugation (UGT1A3, 2B7)	<b>CL increases with dose:</b> 5.0% at 12 mg
<b>Zonisamide</b>	Oxidation (CYP3A4), reduction, acetylation (>50%), renal excretion (30%)	No effect

\*Main route of elimination taken from Johannessen and Landmark [14]. CL/F, apparent clearance; CYP, cytochrome P450; UGT, uridine diphosphate glucuronosyltransferase.

transporters, and had only weak inducing (CYP2B6, CYP3A4, UGT1A1, UGT1A4) and inhibitory (CYP2C8, CYP3A4, UGT1A9, UGT2B7) effects on metabolic enzymes in liver microsomes *in vitro* (Table 4) [1, 2, 7]. The results from our clinical analyses in patients taking adjunctive

perampanel for partial-onset seizures broadly support this pre-clinical profile.

No significant effects of perampanel on the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate and zonisamide were found. Statistically significant, but very weak, effects of perampanel were detected on the clearance of carbamazepine (increased by 4.3%), clobazam (+3.4% in males, +7.7% in females), lamotrigine (+9.3%), and valproic acid (+5.0%), none of which were considered clinically relevant. Indeed, the statistically significant findings may reflect the power of population modelling to detect drug–drug interactions rather than signifying clinically relevant interactions. The technique has extremely high power to detect very small differences. For oxcarbazepine, our model predicted a 26% decrease in oxcarbazepine clearance in patients taking adjunctive perampanel (compared with placebo), but the clinical relevance of this is unknown, as levels of the active metabolite of oxcarbazepine (MHD) were not measured. Based on the official FDA categorization of drug interactions, the effects of perampanel on clearance of carbamazepine, clobazam, lamotrigine, valproic acid do not even reach ‘weak’ induction, and the effect on oxcarbazepine is at the bottom of the ‘weak inhibitor’ range [13]. The mechanism of any interaction with oxcarbazepine is unknown, and cannot be explained by any known effects on metabolic enzymes. Perampanel is predominantly metabolized by CYP3A4 and CYP3A5 enzymes, whereas oxcarbazepine is metabolized to the active monohydroxy metabolite MHD by cytosolic enzymes (Table 3). This requires further investigation.

**Table 4**Inducing and inhibitory effects of perampanel demonstrated in human liver microsomes *in vitro*

CYP1A2	<b>UGT1A1</b>
CYP2A6	<b>UGT1A4</b>
<b>CYP2B6</b>	UGT1A6
CYP2C8	<i>UGT1A9</i>
CYP2C9	<i>UGT2B7</i>
CYP2C19	
CYP2D6	
CYP2E1	
<b>CYP3A4</b>	

Bold text indicates weak inducing effect at up to 30  $\mu\text{mol l}^{-1}$ , italic text indicates weak inhibitory effect at up to 30  $\mu\text{mol l}^{-1}$  [2, 7]. No strong inducing or inhibiting effects were seen.

Perampanel, *in vitro*, was found to be a weak inducer of CYP3A4/5 in liver microsomes (Table 4); therefore, a healthy volunteer study with midazolam was undertaken (midazolam is the recommended probe to explore CYP3A interactions). In that study, statistically significant but small reductions on midazolam  $C_{\max}$  (15%) and AUC (13%) were observed. [7]. Somewhat consistent with this, we saw a small (<5%) increase in clearance of some AEDs that are primarily CYP3A4 substrates (carbamazepine, clobazam) and also of valproate (for which CYP3A4 is not the primary route) [14, 15]; however, we found no effect of perampanel on the clearance of clonazepam and zonisamide, which are also CYP3A4 substrates. These small magnitude effects, and lack of consistency relative to CYP/UGT subtypes, seem to suggest random effects that are reflective of variations in clearance rather than any consistent inducing or inhibiting effect of perampanel on CYP or UGT enzymes.

Our analyses here, along with the PK data from clinical trials, healthy volunteer studies and *in vitro* data from preclinical studies with perampanel indicated no consistent or clinically relevant effects on other AEDs. However, there is some evidence that perampanel can affect the exposure of some drugs, in some patients, but through so far unknown mechanism(s). Perampanel, at a dose of 12 mg/day, has been shown to reduce AUC of levonorgestrel by 40% in a healthy volunteer study in 48 women [1, 2, 7], which cannot be accounted for by any known effects of perampanel on CYP or UGT enzymes, or drug transporters. In addition, a recent publication reported two cases where the addition of perampanel to AED regimens coincided with a large reduction in blood levels of phenytoin in one patient and of rufinamide in another patient, with the development of convulsive status epilepticus [16]. From our analysis in 90 patients taking phenytoin (68 with concomitant perampanel; 22 with placebo), we saw no evidence that perampanel affected phenytoin clearance, but there were insufficient patients taking rufinamide in the perampanel Phase III studies to determine its impact on rufinamide clearance. Theoretically, there is no basis for expecting an interaction with either AED, as perampanel had no known inhibitory or inducing effects on CYP2C9 or CYP2C19, the major enzymes responsible for phenytoin metabolism, or any known strong effects on hydrolysis or UGT enzymes, the main routes of rufinamide metabolism [14]. Known induction or inhibitory effects of perampanel therefore cannot account for these two cases. The only additional route of metabolism that has been explored with perampanel does not help to explain the levonorgestrel result or the two cases above. During its clinical development, perampanel was shown to have no effect on the PK of levodopa (when given in combination with carbidopa as Sinemet<sup>®</sup>, to healthy volunteers), suggesting no interference with decarboxylation or carbidopa's inhibition of decarboxylation [7].

Our report is limited by several factors inherent to using clinical trial data to explore drug interactions. The population reflects the required, and often narrow, eligibility criteria of the clinical trial, so populations of particular interest – e.g. elderly patients and those with multiple concomitant medications – are not well represented in our dataset. Although the PK population was large, only small numbers of patients were taking some of the concomitant AEDs that are now of interest (e.g. rufinamide, in light of the case report by Novy

*et al.* [16]) or newer AEDs that were not frequently used at the time of the clinical trials. The genetic diversity in metabolic enzyme function is likely to be an important contributor to the inter-individual variability in clearance that we saw, but the patient population was not genotyped so this avenue cannot be explored further. It is theoretically possible that, by including only patients who had two quantifiable plasma samples and no changes in concomitant AEDs, our analysis excluded patients who dropped out or adjusted AED dosages because of adverse events caused by perampanel affecting the plasma levels of concomitant AEDs. However, any such patients would have been included in the pooled Phase III analyses, where no patterns in side effects or AE-related discontinuation were evident for any individual concomitant AED. Overall, 9.5% of the Phase III population had AEs that necessitated discontinuation from the study [17].

In conclusion, *in vitro* studies predicted a low potential for perampanel to interact with other drugs, and our population PK analysis of perampanel with concomitant AEDs is broadly in line with this prediction. Perampanel had a small statistically significant effect on the clearance of several concomitant AEDs, but no consistent or clinically notable effect that implicates one particular interaction mechanism for this AED, in our clinical trial population of patients with refractory partial-onset seizures. However, potential interactions via unknown mechanisms cannot be excluded, and it will be valuable to collect information on potential interactions with perampanel in clinical use.

## Competing Interests

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: OM, ZH, AL and JF had support (services of a Medical Writer, Kate Carpenter) from Eisai Europe Ltd, for the submitted work; OM and ZH are employees of Eisai Europe Ltd, Hatfield, UK, and AL and JF are employees of Eisai Inc., Woodcliff Lake, NJ, USA at the time of submission and in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

## Contributors

JF, AL and ZH were involved in designing aspects of the clinical study protocol of the three Phase III clinical trials, and in designing the PK modelling. ZH and OM conducted the PK analyses. KC drafted the outline and the article first draft, and edited and proofread the manuscript. All authors were substantively involved in the preparation of the manuscript, were all involved in interpretation of the data, reviewed all drafts of the manuscript, provided critical appraisal for intellectual content and made changes. All authors approved the final version and accept responsibility for its content.

The clinical studies on which this analysis is based, and the pharmacokinetic analyses, were funded by Eisai Inc., Woodcliff Lake, NJ, USA. Editorial and writing assistance was provided by Kate Carpenter, PhD, and was funded by



Eisai Europe Ltd, Hatfield, UK. The authors are entirely responsible for the scientific content of the paper.

## References

- 1 Eisai Group. Fycompa Summary of Product Characteristics. Hatfield: Eisai Europe Ltd, 2015.
- 2 Eisai Inc. Fycompa US Prescribing Information. Woodcliff Lake, NJ: Eisai Inc., 2014.
- 3 French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, *et al.* Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012; 79: 589–96.
- 4 French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, *et al.* Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013; 54: 117–25.
- 5 Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, *et al.* Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012; 78: 1408–15.
- 6 French JA, Krauss GL, Wechsler R, Wang X, DiVentura B, Brandt C, *et al.* Adjunctive perampanel (PER) for treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients (pts) with idiopathic generalized epilepsy (IGE): a double-blind, randomized, placebo-controlled phase III trial. *Epilepsy Curr* 2015; 15: 367.
- 7 Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. *Epilepsia* 2015; 56: 12–27.
- 8 Gidal BE, Laurenza A, Hussein Z, Yang H, Fain R, Edelstein J, *et al.* Perampanel efficacy and tolerability with enzyme-inducing AEDs in patients with epilepsy. *Neurology* 2015; 84: 1972–80.
- 9 Gidal BE, Ferry J, Majid O, Hussein Z. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures. *Epilepsia* 2013; 54: 1490–7.
- 10 Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Squillacote D, *et al.* Perampanel, a selective, noncompetitive  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 2013; 54: 126–34.
- 11 Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Clément J-F, *et al.* Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307. *Epilepsia* 2014; 55: 1058–68.
- 12 Laurenza A, Ferry J, Hussein Z. Population pharmacokinetics and pharmacodynamics of perampanel: a pooled analysis from three phase III trials (abstract 2.231). *Epilepsy Curr* 2012; 12.
- 13 US FDA. Guidance for Industry: Drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations, 2012. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf> (last accessed 18 April 2016).
- 14 Johannessen SI, Landmark CJ. Antiepileptic drug interactions – principles and clinical implications. *Curr Neuropharmacol* 2010; 8: 254–67.
- 15 Patsalos PN, Fröscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. *Epilepsia* 2002; 43: 365–85.
- 16 Novy J, Rothuizen LE, Buclin T, Rossetti AO. Perampanel: a significant liver enzyme inducer in some patients? *Eur Neurol* 2014; 72: 213–6.
- 17 Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, *et al.* Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia* 2013; 54: 1481–9.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

<http://onlinelibrary.wiley.com/doi/10.1111/bcp.12951/supinfo>.

**Table S1** Population parameter estimates for carbamazepine final PK model

**Table S2** Population parameter estimates for clobazam final PK model

**Table S3** Population parameter estimates for base/final clonazepam PK Model

**Table S4** Population parameter estimates for lamotrigine final PK model

**Table S5** Population parameter estimates for base/final levetiracetam PK Model

**Table S6** Population parameter estimates for final oxcarbazepine PK model

**Table S7** Population parameter estimates for base/final phenobarbital PK Model

**Table S8** Population parameter estimates for base/final phenytoin PK model

**Table S9** Population parameter estimates for base/final topiramate PK model

**Table S10** Population parameter estimates for final valproic acid PK model

**Table S11** Population parameter estimates for final zonisamide PK model